The two papers reprinted in this issue are the first published reports of the successful radioiodine treatment for hyperthyroidism. The story leading up to their publication is an interesting one. The story begins on the twelfth of November, 1936, when Saul Hertz and Earl Chapman, among others, attended a noon seminar at the Harvard Medical School by Dr. Karl Compton of the Massachusetts Institute of Technology entitled "What Physics Can do for Biology and Medicine" [1]. A section dealing with artificial isotopes was presented by Robley Evans, a young colleague of Compton's. It appears that in the course of this presentation, Saul Hertz got the idea that radioactive iodine might be used to study thyroid physiology and pathophysiology. He asked Compton's opinion on the point, and Compton promised to consider the question and get back to him. He did so one month later.

Dear Dr. Hertz:

To my chagrin I have just come across the memorandum which I made on your question about the radioactivity of iodine.

Iodine can be made artificially radioactive. It has a half period of decay of twenty-five minutes and emits gamma rays and beta rays (electron) with a maximum energy of 2.1 million volts. It is probable that there are several other periods of decay, but if so they correspond to types of radioactivity like the one indicated and they are not as yet very definitely established.

Very Sincerely Yours,
Karl T. Compton

A collaboration was established between MIT and the Thyroid Unit of the MGH, and early studies in rabbits were initiated at MIT by Hertz, Evans, and Arthur Roberts who joined Evan's laboratory specifically to work on this project. In 1938, a paper was published in the Proceedings of the Society for Experimental Biology and Medicine showing that radioactive iodine was taken up in the thyroid glands of rabbits, and that the uptake was diminished by exogenous iodine administration and enhanced by the administration of goitrogens [2].

The first attempt at treating Grave's disease with radioactive iodine was made by Hertz and Roberts at MIT in January 1941, and was reported as an abstract in the JCEM in 1942 [3]. In the following months 30 patients were treated with an average dose of 5 mCi followed, 3 days later, by a dose of SSKI. The work was put "on hold" in 1943, the middle of the Second World War, when Hertz left the project to join the navy and Roberts left the Evans lab to work on the development of Radar. Earle Chapman assumed direction of the project in the interim. Chapman changed the protocol to avoid the questions surrounding the relative effects of radioactive iodine versus the SSKI administered on the third day on the course of the hyperthyroidism. He studied 22 patients with radioiodine alone. His collaborator in this work was Robley Evans. In the end, the findings in both studies were the same; radioactive iodine is an effective treatment for Grave's disease. With the end of the war and the return of Saul Hertz to the Thyroid Unit at the MGH, there arose a controversy over the work, who it "belonged" to, and who deserved priority for the idea of treating of Grave's disease with radioactive iodine. Thus arose the interesting approximation of two papers, side by side in the same journal, on the same subject, from the same institution, done in the same period of time, by investigators initially working together on the problem. It smacks of a compromise. But the greater good was well served; these papers mark the beginning of the *rennaisance* in the study and treatment of thyroid disease.

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2. Hertz S, Roberts A, Evans RD: Radioactive iodine as an indicator in the study of thyroid physiology. Proc Soc Exp Biol Med 1938; 39: 510.
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RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

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In previously published experiments of this series [1] radioactive iodine was used as an indicator in the study of animal and human thyroid physiology and iodine metabolism. Much of this preliminary work was done with a view to the discovery of the conditions under which radioactive iodine might be administered with maximum radiational effect in the pathologic thyroid of patients ill with hyperthyroidism. The present paper is a progress report on our early experiences (1941-1946) with such "internal irradiation" in the treatment of 29 cases of hyperthyroidism. It is, indeed, a three to five year follow-up report on these cases.

PROCEDURE

Patients were selected who had had no previous iodine treatment and who were judged clinically to have hyperthyroidism. The usual clinical tests were made and the patients were presented to the Thyroid Clinic of the Massachusetts General Hospital for discussion and determination of their suitability for this type of treatment. In each instance a dose of radioactive iodine, which had been made by the cyclotron at the Massachusetts Institute of Technology or by the Harvard University cyclotron, and separated chemically as sodium iodide, was then orally administered.

The samples of radioactive iodine used were obtained by deuteron bombardment of tellurium and at the time of administration consisted of a mixture of different radioactive isotopes of iodine. Over 90 per cent of the activity at this time consisted of the 12.6 hour isotope I^{130} and most of the remainder of the 8 day isotope I^{131}. The total activity administered varied between 0.7 and 28 millicuries. In 19 cases the total dose was administered to the individual patients as one dose; in 10 cases divided dosages were employed.

From the data already obtained from tracer studies it was considered desirable to keep the total amount of iodide administered below 2 mg. of iodine in order to insure maximum collection by the thyroid.

Urinary iodine excretion was determined during the first seventy-two hours after the administration of radio-iodine. An indirect estimate of the thyroid retention of radioactive iodine was thereby obtained, since an approximate balance exists between administered iodine on the one hand and the sum of thyroid iodine retention and urinary excretion on the other.

Urinary studies were carried out on aliquot portions of carefully collected twenty-four hour specimens, which were kept iced and corked during the collection periods.

It was early found [2] that significant amounts of the original dose were to be found only in the first three days' specimens. Fecal excretion was tested and was found to be so low as to be negligible for the purpose of these experiments.

In a few cases external gamma ray counter measurements were made of the activity of the thyroid of patients following the administration of radioactive iodine. Such measurements are difficult, for obvious reasons, to evaluate quantitatively. However, day to day measurements of this type can give good data on the variation of thyroid iodine content. They were performed in order to follow the loss of iodine from the thyroid following the initial uptake and to evaluate the effect of routine iodinization following the administration of radioactive iodine.

External counter measurements were roughly calibrated against actual direct measurements on the thyroid glands at operation and after chemical separation [2] in 2 patients, previously scheduled for surgery, who received therapeutic amounts of radioactive iodine.

Following the administration of radioactive iodine, routine iodine (nonradioactive) in the usual dosage of saturated solution of potassium iodide 5 minims (0.3 cc.) twice a day was begun at periods varying from one day to several weeks after the radioactive iodine dose.

The basal metabolic rate of the patients treated was tested frequently both before and after the radioactive iodine administration. Basal metabolic levels were taken prior to treatment to establish a measure of the degree of thyrotoxicosis present. In addition to the basal metabolic rate, weights, pulse rates and physical findings were recorded and the total clinical picture was used to evaluate the effects of treatment. No adverse effects, such as fever, nausea or irradiation sickness, were noted in this series of patients. No complaints were recorded regarding the taste of the medicament (since it is tasteless), nor were any local effects, either in the oral cavity or over the thyroid, encountered at the dosage levels used. No increase in the degree of thyrotoxicosis following the radioactive iodine treatment, per se, was recorded, although several test patients were kept uniodinized for three to four weeks prior to routine iodinization.

In most cases, after a period of two to four months following the radio-iodine administration, routine iodine therapy was stopped when an essentially normal basal metabolic rate had been maintained on iodine for a few weeks or months. Such basal metabolic rate response was taken to be indicative of good control of

A report to March 15, 1946.
From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital and the Radioactivity Center, Massachusetts Institute of Technology. This material was presented in part to the American Society for Clinical Investigation in May 1942 (see abstract of proceedings, Physiol. Rev. **62**: 4, 1942). The work was aided by a grant from the John and Mary R. Markle Fund in the names of Professors J. H. Means and Robley D. Evans and was accomplished by close cooperation of the Radioactivity Center of the Massachusetts Institute of Technology, Cambridge, Mass., and the members of the medical staff of the Massachusetts General Hospital, Boston.
This work was performed at the Massachusetts General Hospital and the Massachusetts Institute of Technology under a grant from the John and Mary R. Markle Fund. Cooperation and assistance in this work were given by Professor J. H. Means, Professor J. W. Irvine, Dr. Wendell C. Peacock, Professor M. Stanley Livingston, Professor Robley D. Evans, Drs. R. W. Rawson and Jacob Lerman, the technical assistants Mrs. Phyllis Brown Shattuck, Miss Ann Gaurdo and Miss Mary Lennon as well as the nursing, surgical and medical staffs of the Massachusetts General Hospital. The speech of President Karl T. Compton of the Massachusetts Institute of Technology before a Harvard Medical School colloquium in the fall of 1936 served to inspire the senior author in the initiation of this investigative program.

1. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**: 510 (May) 1938. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, Am. J. Physiol. **128**: 565 (Feb.) 1940; Tr. Am. A. Study Goiter, 1939, p. 260. Hertz, S.: Radioactive Iodine as an Indicator in Thyroid Physiology: III. Observations on Rabbits and on Goiter Patients, Am. J. Roentgenol. **46**: 467 (Oct.) 1941. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: VI. Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation **21**: 624 (Sept.) 1942. Hertz, Roberts and Salter,[2] Hertz and Roberts.[4]

2. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21**: 25 (Jan.) 1942.

the thyrotoxicosis at that time. Failure of the basal metabolic rate to rise on the cessation of iodine treatment was then interpreted as positive evidence of remission of the disease. A rise of the basal metabolic rate on cessation of iodine therapy was considered evidence of failure of the regimen of internal irradiation. A lowered basal metabolic level, with weight gain, symptomatic relief and lowered pulse, were considered indicative of a decrease of the severity of the disease.

As with other forms of treatment for hyperthyroidism, a prolonged follow-up of six months to one year (or more ideally two to five years) following, clinical evidence of remission was required before classification of cases as "cures."

CALCULATION OF RADIATION DOSAGE

In order to obtain a basis of comparison among patients and between radioactive iodine on the one hand and x-ray therapy on the other, the probable values of radiation dosage delivered in the thyroid were calculated. Such calculations are based on the following data:

1. Fractional uptake of radioactive iodine by the thyroid.
2. The known energy of the radiations from I^{130} and I^{131}.
3. The clinical estimation of the weight of the thyroid of the patient.
4. The known pattern of uptake and retention of radioactive iodine [3] by the hyperplastic thyroid gland of hyperthyroidism.[2]

By using the known values of ionization produced by 1 millicurie of radiation and the properties of I^{130} and I^{131} the following formulas can be derived for the total radiation delivered in decaying to zero:

$$\text{Radiation (in roentgen units)} = \frac{10{,}000 \text{ (dose of } I^{130} \text{ in mc) (fractional uptake in thyroid)}}{\text{weight of thyroid in grams}}$$

For I^{131} the constant 10,000 is replaced by 117,000. Thus for I^{130} a net collection of 3 millicuries in a 30 Gm. thyroid will give a total of 1,000 roentgens in decaying to zero.[4]

The effectiveness of radiation therapy is known to depend on the rate of delivery, especially at low rates. In the case of I^{130} the initial rate of delivery of a 1,000 roentgen dose is 55 roentgens per hour. For I^{131} it is only 3.6 roentgens per hour. Thus, while in these experiments the total radiations delivered by the two isotopes are comparable, the rate is so much slower for the long-period isotope that its effectiveness is at least open to question. Furthermore, an appreciable fraction of the activity leaves the thyroid during the decay of the long period iodine.[2] We shall assume throughout that it is the I^{130} radiation which is most effective.

Calculations of the type described are subject to large errors. These arise mainly in the estimate of the thyroid weight, in the determination of thyroid iodine uptake and in the assumption of a uniform picture of iodine retention.[2] Errors of 50 per cent or more in the estimate of the thyroid radiation are therefore to be expected.

3. This pattern was determined by the use of tracer quantities of radioactive iodine. It is not strictly correct to assume, as we have, that the pattern will be the same when quantities of activity sufficient to have a biologic irradiation effect on the thyroid are present. However, in the absence of other data we have assumed that the pattern is the same. If this is in error it will introduce another error into the calculation, already admittedly approximate, of the dosage delivered to the thyroid.

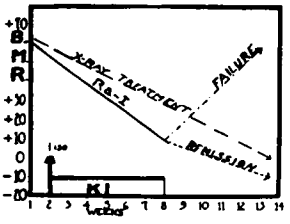
4. The millicurie values of activities cited in this paper are absolute values based on the number of disintegrations occurring in the radioactive substance, determined by methods like those described by Deutsch, M.; Downing, J. R.; Elliott, L. G.; Irvine, J. W., Jr., and Roberts, A.: Physical. Rev. **62**: 4, 1942.

RESULTS

The accompanying graph is a schematic representation of the expected course of the basal metabolic rate in successfully and unsuccessfully treated cases. The upper broken line represents the course of the basal metabolic rate of a patient treated successfully by means of orthodox external x-ray therapy. The latter is given as a basis for comparison of the time interval required for obtaining a remission by the internal and external forms of thyroid irradiation in typical cases of hyperthyroidism.

The results obtained with 29 patients are summarized in tables 1 and 2. Table 1 affords an analysis of 9 cases in which cure was not obtained by the radiational effect of radio-iodine. Table 2 gives an analysis for 20 cases considered to be cures. These cases are so classified after follow-ups and examinations extending to March 1946.

The excretion studies and the external gamma ray counter measurements showed early in these experiments that there is no peak in the excretion of iodine in any of 14 cases tested, nor is there any sudden drop in the radioactive iodine content of the thyroid when a patient who has been given radioactive iodine is started on routine iodinization. On the contrary, these experiments showed that iodinization either has no effect on the normal slow loss of iodine from the thyroid or tends to "freeze" the radioactive iodine collected by the gland, i. e. to foster its longer retention therein. As much as 25 per cent of the initially collected radioactive iodine may remain in the thyroid twenty-five days after an initial collection and subsequent iodinization.[2] It is clear that such prolonged retention is advantageous from the standpoint of efficient use of the radioactive isotopes administered. Urinary studies in a typical case gave the results recorded in table 3.



Course of the basal metabolic rate in successfully and unsuccessfully treated cases of hyperthyroidism: solid line, treatment by radioactive iodine; upper broken line, treatment by external x-irradiation. The arrow indicates the point at which I^{130} was administered to the patients treated with radioactive iodine. The lower rectangle indicates the administration of ordinary iodides. A rise in the basal metabolic rate on omission of iodide therapy is significant of continued thyrotoxicity and failure of the therapeutic program; the absence of any such rise in any case is interpreted as evidence of remission of the disease as a result of the type of treatment received by the patient.

The reasons for adopting the procedure of full iodinization following the radioactive iodine dose were, in the main concern, that if the radioactive iodine was not effective the patients might be injured by uncontrolled thyrotoxicosis. In addition, no adequate control was possible of the iodine intake of patients (from extraneous sources) while ambulatory and awaiting the radiotherapeutic effect.

In spite of the fact that the interpretation with regard to cure might be rendered slightly less unequivocal with the use of this procedure, one can depend on the familiar fact that routine iodinization, per se, has been known for years to be a rather unsatisfactory sole treatment for the great majority of unselected thyrotoxic patients.[5]

5. Thompson, W. O.: Toxic Goitre: The Present Status of Treatment, Canad. M. A. J. **42**: 214 (March) 1940.

COMMENT ON RESULTS OF TREATMENT

A total of 29 patients were given radio-iodine in quantities which might be presumed, a priori, to have a therapeutic effect. As might be expected, in the earlier cases the dosage administered was not uniformly effective. At the time of starting these experiments there was no accumulated experience as to the possible adverse general effects of the administration of radioactive isotopes of iodine on the internal human economy. As our experience became extended, the total activity administered was increased from values in the vicinity of 1 millicurie to a maximum of 28 millicuries in 1 case without the occurrence of even temporary immediate reaction. As the series was followed, no clinical evidence has appeared to make us consider that there are any such undesirable effects or dangers in the range of activities used. No case of cancer of the thyroid has occurred; it appears unlikely that any such condition will arise from the internal irradiation involved in this form of treatment at the activity levels used.

Although the error in the estimation of the actual dosage delivered to the thyroid on the basis of the method of estimation used is necessarily large, it is possible, from the clinical behavior of the latter part of our series, to select the region near 1,000 roentgens (of the 12 hour isotope) as the minimum biologically effective range of dosage. In case 2 four separate doses of 1.4, 0.9, 2.4 and 0.8 millicurie were given to a patient with an uniodinized thyroid, with a frank failure of this regimen. The total dose in this case was 5.5 millicuries and the thyroid irradiation 500 roentgens (of 12 hour radio-iodine).

FAILURES

In case 10 (0.7 millicurie), in which operation was performed, the failure of the regimen may be attributed to the use of subminimal doses of radio-iodine. In cases 1, 5, 14, 16 and 19 of table 1 operations were performed following the administration of 3.3, 5.7, 15, 10 and 28 millicuries respectively. These were the only cases in the series in which operations were performed, and in every 1 of these 5 cases postoperative myxedema or hypometabolism ensued. In case 14 the basal metabolic rate was —15 the day before operation; it was essentially normal in the others (on iodides).

The occurrence of postoperative hypometabolism in 100 per cent of patients exhibiting essentially normal basal metabolic rates preoperatively is suggestive of a radiational effect on the thyroid tissue remaining after operation. For example, Mrs. R., patient 5, who was operated on after receiving 5.7 millicuries (1,000 roentgens) in a planned experiment for another purpose, developed myxedema despite the fact that one of us was present to advise the surgeon to leave 6 to 7 Gm. of thyroid (a nonradical subtotal thyroidectomy) in view of the previously demonstrated high radio-iodine uptake by this patient's thyroid. It is reasonable to surmise that hypometabolism might not have ensued in such a large percentage of the patients had they not received the radio-iodine prior to operation.

An analysis of preoperative basal metabolic rates of the patients operated on indicates that all 5 so treated were adequately controlled on iodides at the time of operation despite the long period of observation of these patients in a nonoperated state.

TABLE 1.—*Analysis of Nine Cases of Hyperthyroidism in Which Cure Was Not Effected by Administration of I^{130} with Therapeutic Intent*

Number	Patient	Basal Metabolic Rate Level Prior to I^{130}	Dose of I^{130} and Dates of Administration	Basal Metabolic Rate Prior to Subtotal Thyroidectomy	Postoperative Basal Metabolic Rate	Thyroid Weight, Gm.	Histologic	Total Thyroid Irradiation (Roentgens) 12 Hr. I^{130}	Total Thyroid Irradiation (Roentgens) I^{131} 8 Day	Estimated Thyroid Weight	Percentage of Dose of Radio-Iodine Excreted 72 Hours
1	Elizabeth D.	+30	2.1 mc. 3/31/41 1.3 mc. 4/16/41 3.4 mc.	(—5) (—7)	(—29)	34.5	Involution	470 220	660 240	35	20 28
5	Lillian R.	+35	5.7 mc. 7/16/41	Planned experiment	(—20)	31.8	Hyperplasia, no involution	1,000	1,150	40	27
10	Gladys B.	+55	0.7 mc. 2/2/42	Controlled through pregnancy (+3) (12/30/43)	(—26)	26 30 56	Hyperplasia + moderate involution	120	80	60	38
14	Wilfred B.	+50	15 mc. 7/15/42	(—15) (8/17/43) operation (8/18/43)	(—24)	55	Hyperplasia + involution	650	...	60	71 (?)
16	Carmella D.	+25	10 mc. 8/11/42	(—8)	(—24)	28	Involution	1,800	...	45	6
19	Peter C.	+65	15 mc. 8/25/42 8 mc. 3/8/43 5 mc. 3/9/43 28 mc.	(+8) to (+13)	(+36) to (—18)	35	Slight hyperplasia + involution	2,000 (?) 1,500 (?)	...	60	9 15 (?) 7
2	Margaret B.	+35	1.4 mc. 5/10/41 0.9 mc. 41 2.4 mc. 42 0.8 mc. 42 5.6 mc.	Persistent thyrotoxicosis, another radio-iodine dose proposed	....	Not operated on		160 110 120 100	140 100 120 100	40	54 48 78 ..?
4	Camille Sch.*	+30*	3.6 mc. 7/14/41 2.2 mc. 7/31/41 5.8 mc.	Eyes better, no goiter, basal metabolic rate 4 yrs. off all medication	(+2)	Not operated on		270 170	300 180	60	55 56
3	Ruth M.	+50	3.4 mc. 6/6/41 20 mc. 1/9/46	Remission of one year's duration following hemithyroidectomy (6/25/41) (Recently for true recurrence)				430 4,300	410	45 30 (recurrence)	45 35

* Case classified as special ophthalmopathic type of hyperthyroidism (Low intake of I^{130}).
Eight day isotope figures assume no loss of iodine from thyroid during decay; they are therefore excessive. They were not measured for cases 13-29.

Mrs. M. B., patient 2, has been taken off iodine in preparation for a 20 millicurie dose of radio-iodine. She has remained fairly well, at work, on full iodinization but remains chronically thyrotoxic.

Miss R. M., patient 3, who had 3.4 millicuries, was subjected to hemithyroidectomy in June 1941. She was in remission off iodides for twelve months but during the past one and one-half years developed a definite recurrence of hyperthyroidism, for the treatment could have been by subtotal thyroidectomy, since the probability of recurrence is distinctly higher following pregnancy in the postoperative follow-up of surgically treated cases.

One patient (4, Mrs. C. S.) should, in our opinion, be excluded from the series on the grounds of failure to present a picture of typical toxic diffuse goiter. As our experience developed it became evident [6] that patients in the "special ophthalmopathic group" [7] char-

TABLE 2.—*Analysis of Twenty Cases of Hyperthyroidism Successfully Treated with Therapeutically Sufficient Dosage of I^{130} Followed by Ordinary Iodide Administration*

Number	Patient	Dose of I^{130} and Date of Administration	Basal Metabolic Rate Before I^{130}	Basal Metabolic Rate Level Off Iodides	Time Off Iodides	Thyroid Size, 1946	Estimated Thyroid Weight, Gm.	Percentage of Radio-Iodide Excreted, 72 Hours	Estimated Thyroid Irradiation (Roentgens) 12 Hour	Estimated Thyroid Irradiation (Roentgens) 8 Day
6	Michael K.	2.3 mc. 7/24/41 1.7 mc. 7/30/41 4.0 mc.	45+	12/—/42 (— 9) 5/—/43 (—16) 1/—/46 (— 7)	4 yrs.+	N	45	35 22	320 280	390 300
7	Allison D. (aged 9)	1.4 mc. 9/19/41 1.5 mc. 9/21/41 2.9 mc.	65+	1/ 8/46 (— 6)	4 yrs.	N	45	9 20 (?)	260 260 (?)	230 220 (?)
8	Naomi K. (aged 9)	1.5 mc. 9/24/41	30+	7/17/45 (— 3)	Months	Firm 2 × N	40	15	300	250
9	Mildred G.	4.9 mc. 11/26/41	30+	5/ 8/45 (—10)	4 yrs.	N	60	17	650	420
11	Frances H.	5.8 mc. 4/ 9/42	37+	7/ 9/42 (—12) 2/24/44 (+ 9) 2/ 3/46 (—21)	3.5 yrs.	N	60	17	750	380
12	Ferdinand L.	7.5 mc. 5/15/42	55+	45 (+11) 2/ 3/46 (—13)	3 yrs.	Hard 1.5 × N	60-75	26	950	500
13	Dorothy P.	12 mc. 6/ 9/42	30+	3/—/43 (+ 6) 2/ 3/46 (—10)	3 yrs.	N	40	71	750	
15	Mary M.	6 mc. 8/11/42 4 mc. 8/11/42 10 mc.	35+	4/—/45 (— 6) 2/ 3/46 (+ 2)	Months	N	40	10	2,000	
17	George T.	13 mc. 8/13/42	50+	44 (—15) 1/ 6/46 (— 9)	3 yrs.+	N	60 (50-75)	14	1,300	
18	Jeanette G.	10.5 mc. 8/15/42	35+	8/22/44 (+11) 2/16/46 (+ 5)	3 yrs.+	N	30-40	15	2,000	
20	Anne D.	10 mc. 11/14/42	50+	4/ 3/45 (— 1) 2/16/46 (— 5)	2 yrs.+	N	45	20	1,600	
21	Richard T.	14 mc. 11/20/42	+45	1/ 8/46 (—13)	3 yrs.+	N (Dr. H. L. Blumgart)	50	15 (?)	2,000	
22	Esther R.	13 mc. 3/ 9/43	+20	6/30/43 (— 8)	2 yrs.+	"? N" (L. M. D.)	35	33	2,200	
23	Margaret D.	8 mc. 3/15/43 10 mc. 3/16/43 18 mc.	+55	6/ 9/43 (—11) 2/16/46 (— 3)	2 yrs.+	Firm 1.5 × N	75	76 67	500	
24	Jane Anne F.	10.5 mc. 3/26/43 4.5 mc. 3/27/43 15 mc.	+40	12/—/45 (— 5)	2 yrs.+	N (Dr. J. C. Zilhardt)	50	57 (?) 31 (?)	1,000 approximately	
25	Sophie R.	16 mc. 4/ 2/43	+44	9/28/44 (— 7) 4/27/45 (+ 9)	2 yrs.+	N (Dr. J. C. Aub)	50	20.6 63.0	750 approximately	
26	Bessie W.	12 mc. 4/ 6/43	+39	45 (— 8) 1/16/46 (+ 2)	2 yrs.+	N	45	85	350	
27	Winifred K.	13 mc. 4/12/43	+40	7/17/45 (—16) 2/15/46 (—10)	2 yrs.+	N	50	33	1,600	
28	Margaret H.	10.5 mc. 4/13/43 11.0 21.0 mc.	+56	12/—/45 (—15) 2/ 3/46 (+ 6)	2 yrs.+	N	75	.. (?)	2,000 approximately	
29	Julia Laf. Ry.	8 mc. 3/29/43 4 mc. 3/30/43 12 mc.	+30	2/—/46 (— 5)	2 yrs.+	N	55	10 53 (?)	1,200 250	

Eight day isotope figures assume no loss of iodine from thyroid during decay; they are therefore excessive. They were not measured for cases 13-29.

of which she received 20 millicuries of radio-iodine on Jan. 9, 1946.

In case 10 a temporary control of the disease was achieved, but a true recurrence of the disease following an uneventful pregnancy occurred, for which surgical treatment was given at the United States Naval Dependents' Hospital, Boston. As this patient did not remain "cured" for over a year, she is not included in the series of cures. In comparing her case with others in which routine surgical treatment was administered, she might be considered as at least having been temporarily benefited to the same extent by radio-iodine as she acteristically had lower thyroid uptakes of radioactive iodine than patients with typical hyperthyroidism. Although this patient has done well without operation, her improvement cannot be ascribed to the radioactive iodine treatment. In our experience this group does well on medical therapy in any event [8] and rather poorly

6. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: V. The Use of Radioactive Iodine in the Differential Diagnosis of Two Types of Graves' Disease, J. Clin. Investigation **21**: 31 (Jan.) 1942.

7. Hertz, S.; Means, J. H., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, West. J. Surg. **49**: 493 (Sept.) 1941; Tr. Am. A. Study Goiter, 1941.

8. Means, J. H.: The Eye Problems in Graves' Disease, Illinois M. J. **80**: 135 (Aug.) 1941.

by rapid cure of the thyrotoxic element by operation. It is conceivable, however, that by giving larger dosages of radioactive iodine radiotherapeutic advantage could be obtained even in this class of cases.

In summary, therefore, there were 9 cases which comprise this series of "failures."

In 1 case (10), in which there was a recurrence, the dosage of radio-iodine is known to have been probably inadequate (120 roentgens) for biologic effect. One, patient 4, is grouped in this list because she was a "special ophthalmopathic" patient; the control of her disease cannot be uniquely attributed to the effect of the radio-iodine.

Two patients (3 and 5) had operations as part of planned experiments and gave us the first evidences of possible biologic effect of the radio-iodine which was administered. They are, however, included among the failures because of the complicating factor of operation. Patient 5 developed myxedema; patient 3 suffered a recurrence after hemithyroidectomy.

Five patients (1, 5, 14, 16, 19) were operated on who had received dosages of radio-iodine from which one might expect a cure. All developed postoperative hypometabolism.

Mr. P. C., patient 19, received divided dosage of 15, 8 and 5 millicuries, the largest total dosage in our series. He developed postoperative hypometabolism after a short period of persistent thyrotoxicosis (basal metabolic rate + 36 to — 18). His basal metabolic rate the day prior to operation was + 13.

TABLE 3.—*Urinary Studies*

Radio-iodine (20 mc. of I^{130}) orally administered as a single dose; 37 per cent excreted in a period of four days (I, II, III, IV = twenty-four hours' collections of urine following the radio-iodine).

I. 27.9%. 0.047%/cc./hr.	
II. 3.3%, 0.006%/cc./hr.	
	5 minutes of saturated solution of potassium iodide
III. 3.45%, 0.006%/cc./hr.	
	5 minims of saturated solution of potassium iodide
IV. 2.37%, 0.0001%/cc./hr.	

Finally, patient 2 received a total of 5.5 millicuries of radio-iodine in four divided doses, with a total radiation of 500 roentgens. She has not been operated on but exhibits clear evidence of continued thyrotoxicosis which is only moderately well controlled by iodine.

SUCCESSES

There were a total of 29 cases in this entire series. In 1 case (10) the dosage was subminimal. Of the remaining 28 patients who received radio-iodine of therapeutic intensity, 5 were subtotally thyroidectomized. All 5 developed hypometabolism.

In the remaining 23 cases in which radio-iodine of therapeutic intensity was given, no subtotal thyroidectomy was performed. In 20 of these patients a recent follow-up indicates that they are no longer thyrotoxic. The remaining 3 cases (2, 3 and 4, already discussed) cannot be considered as successes.

The thyroid gland in all but 3 of these patients became normal in size (impalpable). In the 3 patients in whom the thyroid is still palpable, despite general metabolic and clinical cure (off iodine), there were decided reductions in the size of the goiters. They have firm to hard glands which suggest the presence of chronic thyroiditis or fibrosis. These patients had the largest pretreatment goiters. One of them (12) states that his collar size has now returned to the same as he had worn prior to the onset of hyperthyroidism. He had had a large goiter (three times normal size) prior to treatment.

In addition to the 20 cures in which operation was not performed, there is pathologic evidence for cure in 1 case (16) in which operation was performed. A 28 Gm. thyroid was removed; it showed histologic "involution," and myxedema subsequently developed.

There were no mortalities in the series either as a result of thyrotoxicosis or due to operation in the 5 cases. The incidence of myxedema and hypometabolism has been mentioned.

No undesirable complications such as tetany or loss of phonation occurred. No tracheal or laryngeal irritations occurred. No undesirable radiation effects were observed. No anemia ensued in any patient in the series.

Although 5 of the 20 patients not operated on developed basal metabolic levels of — 15 to — 20, no one suffered the development of permanent myxedema at the dosage level employed in this series.

CONCLUSIONS

From these data it is clear that we are now in a fair position to set down a minimum dosage and a preliminary estimation of the therapeutically effective dosage range in typical cases of hyperthyroidism. This range is from 5 millicuries to 25 millicuries (as a single dose), with the choice of the dose largely a function of the clinical estimation of the size of the goiter of the patient being treated.

The calculated dosages administered in those cases (500 to 2,500 roentgens) (± 50 per cent) in which treatment was successful are in satisfactory agreement with the x-ray dosages which have been successfully used (1,000 to 1,200 roentgens). The apparently greater efficacy of the radio-iodine treatment as compared with orthodox x-ray treatment may perhaps be attributed to the fact that x-ray dosages are sometimes limited by the appearance of undesirable skin reactions; and the intraglandular irradiation within the thyroid cells may conceivably offer certain advantages over external irradiation. On the basis of our experience to date, the following are considered to be important clinical considerations in patients who are to be chosen to undergo treatment by radioactive iodine:

1. No previous iodine therapy; or, if previously treated, iodine treatment to be stopped for at least one month to allow maximum uptake of the radioactive iodine dose.[2]
2. Availability for close follow-up.
3. Administration of routine iodinization, starting one to three days after the administration of radio-iodine, as soon as the uptake is known to be adequate.
4. Unwisdom of treating patients having large goiters with secondary involutional changes at this time by this means, as surgery might be needed by them on a purely mechanical basis, even though detoxification by radioactive iodine could be accomplished. Early diagnosis and early treatment of cases would then appear to offer major advantages in this as in many other forms of treatment.

The treatment of the special cases in the ophthalmopathic group of hyperthyroidism appears to offer special problems, as do cases of large, involutional goiters. However, typical cases of hyperthyroidism respond to this form of treatment in such a manner as to make it possible to venture the prediction that this therapeutic program may in time replace the surgical approach currently in vogue.

Radioactive iodine is produced in enormous quantities in nuclear chain-reacting piles. When radio-iodine from such sources is made readily available to the medical

profession, this form of treatment may well prove itself not only highly effective, safe and noninjurious but also cheap and of least inconvenience to the patient who may receive it while continuing at his normal pursuits. After a short period of hospitalization for the usual preliminary clinical studies and the administration of radio-iodine, the patient may be fully iodinized and released, to be followed as an ambulatory case.

SUMMARY

On the basis of a series of animal and clinical experiments using radioactive isotopes of iodine as a tracer in the study of thyroid physiology and iodine metabolism, the treatment of 29 cases of hyperthyroidism with internal irradiation by radioactive iodine was instituted. By careful excretion studies, external counter measurements over the thyroid gland and by planned operations in 2 cases, data were obtained which allow us to construct a formula for a procedure in treatment.

The addition of ordinary iodine therapy after the administration of radio-iodine offers many advantages in the clinical care of these patients and in the economy and safety of the procedure.

By an analysis, over a long period, of both the failures and successes in this series of 29 cases, it is shown that radioactive iodine when given in the dosage range of 5 to 25 millicuries to uniodinized patients with hyperthyroidism possessing goiters of 60 to 75 Gm. is highly effective as a cure of the disease in about 80 per cent of cases. When appreciable activity has been administered and subtotal thyroidectomy is resorted to, myxedema or hypometabolism may be expected to develop in a large fraction of the cases (100 per cent in 5 cases in this series).

THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

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Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Means and Holmes [1] pointed out that in this form of treatment about one third of the patients are cured, another third improved and another third not affected. Since 1923 ordinary iodine by mouth has been used as a preoperative method of quieting the hyperactive thyroid in preparation for surgery. Under iodine alone occasionally the patient and the doctor have been agreeably surprised to find that the symptoms and signs of hyperthyroidism disappeared, and a permanent remission apparently was effected. That x-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that some day a more effective, nonsurgical agent would be found. Then the MacKenzies [2] and Astwood [3] discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been investigated, and until now thiouracil has been found to be most useful in the treatment of thyrotoxicosis.

Induced radioactivity was discovered in 1934, and that same year Fermi and his co-workers [4] in Italy prepared radioactive isotopes of iodine. Because the thyroid absorbs iodine selectively, it seemed likely that beta rays from iodine rendered radioactive would have a greater radiation effect than that derived from roentgen rays delivered through the skin and overlying tissues.

The use of radioactive iodine in the study of thyroid physiology was soon undertaken and reported first in 1938 by Hertz, Roberts and Evans.[5] Subsequently these and other investigators used various isotopes of radioactive iodine as tracers for the study of thyroid function [6] and it was found that in untreated hyperthyroidism the thyroid may take up as much as 80 per cent of a small dose (less than 2 mg.) of iodide within a few hours after oral administration.[7] This established the basis for therapeutic trials of radioactive iodine, and in 1942 Hertz and Roberts [8] published a preliminary report of the treatment in this manner of 10 patients. In this series the procedure was to give the radioactive iodine and follow this with ordinary iodine by mouth for a period of several months. However, our review in the clinic of these 10 cases of Hertz and Roberts, and an additional 18 so treated under the direction of Hertz, has led to the conclusion that it is difficult to decide whether those patients who improved were responding to the ordinary iodine, to the radioactive iodine or to their combination. The dosage of radioactive iodine given to these 28 patients averaged 5 millicuries in 1941, 10 millicuries in 1942 and 14.5 millicuries in 1943, the largest single dose being 21 millicuries. In April 1943 Dr. Hertz went on active duty in the Navy and asked us to continue with this study. The present report is on a series of 22 patients with hyperthyroidism treated only with radioactive iodine and with considerably higher doses. Although both Hertz and Roberts [8] and Hamilton and Lawrence [9] were encouraged by their therapeutic trials, the details of their findings have not yet been published.

METHODS AND DOSAGE

Selection and Care of Patients

The patients selected in the Thyroid Clinic of the Massachusetts General Hospital for radioactive iodine therapy were judged by several physicians to be thyrotoxic on the basis of classic disease pattern accompanied with constantly elevated basal metabolic rates. All patients had thyroids estimated to be at least two to three times normal in size. All but 3 were kept free from all forms of treatment, especially iodine, for at least four weeks prior to giving radioactive iodine. For the administration of the drug they were usually hospitalized for a time adequate to obtain levels of their basal metabolic rate, then given radioactive iodine by mouth—simply a drink of what tastes like rather stale water.

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From the Thyroid Clinic of the Massachusetts General Hospital (Dr. Chapman) and the Radioactivity Center of the Department of Physics of the Massachusetts Institute of Technology (Dr. Evans).

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9. Hamilton, J. G., and Lawrence, J. H.: Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine, J. Clin. Investigation **21**: 624 (Sept.) 1942.

The urine was then collected for a period of three days to measure the urinary excretion of radioactive iodine.

Preparation of Radioactive Iodine

The radioactive iodine is prepared by the nuclear bombardment of metallic tellurium, in the Massachusetts Institute of Technology cyclotron, using 14 MEV (million electron volts) deuterons. This bombardment transmutes tellurium into iodine. The principal isotopes produced in this way are I^{130} (half period 12.6 hours) and I^{131} (half period 8.0 days). Immediately after a short bombardment the 12-hour iodine has about ten times the radioactivity of the 8-day iodine isotope which is produced simultaneously. The ratio of 12-hour to 8-day iodine decreases with increasingly long bombardments. For the preparation of therapeutic radioactive sources the bombardments were usually about three to ten hours in duration.

Following the bombardment, the radioactive iodine is separated [10] from the target. To the metallic tellurium is added 0.5 mg. of iodine as potassium iodide and 25 cc. of 3 molar sulfuric acid. Then concentrated nitric acid is added dropwise while the solution is heated. This dissolves the target and causes the iodine to distil over as elementary iodine, which is collected in carbon tetrachloride. The carbon tetrachloride solution is washed once with water in a separatory funnel and then the iodine is reduced with sodium bisulfite and is extracted in an aqueous layer as sodium iodide. This aqueous solution is filtered to remove any residual droplets of carbon tetrachloride.

The final solution presented to the patient is distilled water containing 14 to 79 millicuries [11] of 12-hour iodine and about one-tenth that amount of 8-day iodine in 0.5 mg. of iodine as sodium iodide. Because of the rapid decay of the 12-hour isotope, which is the more important radiation source, all preparations were administered to the patients within one to four hours after the conclusion of the bombardment. The doses in table 2 are in terms of the radioactivity of the 12-hour isotope at the time of administration.

Tissue Radiation Doses

In the therapeutic use of x-rays, the radiation doses are commonly reported in roentgens. The x-rays produce high-speed secondary electrons in the tissue, and the therapeutic effect of x-rays is actually due to the interaction of these secondary electrons with the tissues. The beta rays from a radioactive isotope are also high-speed electrons. These beta rays can therefore be expected to produce tissue effects similar to those produced by x-rays, and the radiation dosages can also be expressed in roentgen units. The beta rays have a maximum range of only a few millimeters of tissue. Therefore the radiation doses are confined almost exclusively to the tissue actually containing the radioactive isotope and are proportional to the concentration of the isotope in the tissue.

The tissue radiation dose may be predicted quantitatively for an average patient in terms of the number of millicuries of 12-hour iodine administered per estimated gram of thyroid tissue. Patients may show wide variations from this estimated average tissue radiation dose, especially because of individual variations in the retention of radioactive iodine. It is assumed that substantially all the administered iodine is either taken up by the thyroid gland or excreted in the urine. A high urinary excretion of radioactive iodine indicates a correspondingly low retention of iodine by the thyroid, with a consequent reduction in the radiation dose available to the gland.

The tissue radiation dose delivered to the thyroid gland can be estimated from the shape of the iodine retention curve,[7] the measured fractional urinary excretion of radioactive iodine, the radioactive decay curve of the two isotopes involved and the roentgen equivalent [12] of the energy of the radiation from the two isotopes.

A concentration of 1 mc. (3.7×10^7 disintegrations per second) of 12-hour iodine per gram of thyroid tissue delivers 12.3 roentgens per minute. If 0.1 mc. of 8-day iodine is also present per gram of tissue this will add 0.85 roentgen per minute.

As an illustration, we shall estimate the radiation delivered to the thyroid by the 14 millicurie dose given to patient 1. Urinary excretion measurements showed that this patient excreted about 25 per cent of the dose in three days. This patient received 14 mc. of 12-hour iodine and about one tenth as much 8-day iodine. The thyroid was estimated to weigh 40 Gm. If all the administered iodine should be concentrated in the thyroid ($R = 1.00$) the initial dosage rate A_0 would be $12.3\ (14/40) = 4.30$ roentgens per minute from the 12-hour iodine plus $0.85\ (14/40) = 0.30$ roentgen per minute from the associated 8-day isotope.

TABLE 1.—*Estimation of Roentgen Tissue Dose Due to 12-Hour Radioactive Iodine*

Assumes a maximum of 80 per cent uptake of a dose of 0.35 millicuries per gram of thyroid.

Time Interval, t_1 and t_2	Fraction of Administered Iodine Retained in Gland (7), R	Fraction of Original 12-Hour Radioactivity Remaining: At Beginning of Time Interval, F_1	At End of Time Interval, F_2	$F_1 - F_2$	Dose in Interval, $D = 4680R\ (F_1 - F_2)$	Total Dose in Tissue, Roentgens Due to 12-Hour Iodine
0 - 12 hr.	0.80	1.00	0.52	0.48	1,780	1,780
12 - 24 hr.	0.80	0.52	0.27	0.25	940	2,720
24 - 36 hr.	0.73	0.27	0.14	0.13	440	3,160
36 - 48 hr.	0.54	0.14	0.073	0.07	180	3,340
48 - 60 hr.	0.48	0.073	0.038	0.035	80	3,420
60 - 72 hr.	0.43	0.038	0.020	0.018	37	3,457
72 - 84 hr.	0.41	0.020	0.010	0.010	19	3,476
84 - 96 hr.	0.39	0.010	0.0063	0.0063	9	3,485
96 - 108 hr.	0.38	0.0063	0.0028	0.0027	5	3,490
108-120 hr.	0.37	0.0028	0.0014	0.0014	2	3,492

The constant coefficient of the equation [13] for determining the total roentgen ray dosage due to the 12-hour isotope is $1.44\ TA_0 = 1.44 \times 12.6 \times 60 \times 4.30 = 4{,}680$ roentgens. The dosages delivered in each 12-hour interval are given in the last column of table 1. It will be noted that 50 per cent of the total radiation dose from the 12-hour isotope is delivered in the first twelve hours, and 90 per cent is delivered within the first thirty-six hours after administration. The tissue dose per hour is mainly due to the 12-hour isotope for the first 2.5 days. Thereafter the 8-day isotope adds approximately 2 per cent each day to the total radiation previously delivered by the 12-hour isotope.

In the previously treated patients [8] the use of low doses, below 10 mc., was thought by us to explain the lack of improvement in several patients, so it was decided to increase greatly the dose and if possible to

10. Professor John W. Irvine Jr. and Mrs. Elizabeth Pattison carried out these radiochemical procedures.
11. A millicurie is 37,000,000 atoms disintegrating per second.
12. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, Tr. Am. A. Study Goiter, 1939, p. 260.
13. See full paper, available in reprint form.

TABLE 2.—*Summary of 22 Cases of Hyperthyroidism Treated Only With Radioactive Iodine*

	Before Treatment					Treatment: Radioactive Iodine				Response to Treatment: Last Examination			
Case	Age	Sex	Thyroid Size, Estimated in Grams and X Normal	Basal Metabolic Rate Level	Weight, Kg.	Dose, mc.	Date	Excretion † % in 3 Days * in 2 Days	Estimated, mc./Gm.	Interval to Normal Basal Metabolic Rate	Basal Metabolic Rate; Date	Weight, Kg.	Size of Thyroid	Comment
1. E. W.	49	♂	40 2x 20 1x	+36	58	14 mc. 21 mc.	5/18/43 9/24/43	25% 100%	0.35 1.00	2 mos.	+8 2/5/46	67	1 x	See details in case report
2. M. M.	38	♀ Negro	120 6x 120 70 3x	+55	47	15 mc. 53 mc. 79 mc.	6/ 2/43 8/17/43 9/29/43	.... 35% 49%	0.12 0.44 1.12	See fig. 1	+12 2/21/46	57	....	See details in case report
3. A. M.	34	♂	40 2x	+26	67	18 mc.	8/24/43	....	0.45	6 wks.	—10 1/15/46	68	1 x	X-ray treatment in February 1943 while on iodine; no response; by October 1943 in myxedema, same through 1944-1945
4. B. O'L.	52	♀	65 3x	+47	57	18 mc. 22 mc. 20 mc.	8/24/43 9/ 7/43 9/21/43	.... 11% 10%	0.27	4 mos.	+7 12/15/45	60	1 x	B. M. R. normal by December 1943; remained well through 1944 and 1945
5. H. S.	50	♀	30 2x	+30	41	20 mc. 27 mc.	8/24/43 11/ 9/43	.... 62%	0.66	6 wks.	—5 9/18/45	59	1 x	Subtotal thyroidectomy 1930; recurrence 1943; B. M. R. normal 11/9/43; gained 10 Kg. 1 year; well through 1945
6. F. B.	55	♂	55 3x	+46	66	30 mc. 25 mc. 54 mc.	12/ 2/43 12/16/43 7/ 5/44	16% 54% 83%	0.54	4 wks. 4 wks.	+26	.. 75	... 1 x	Very toxic with auricular fibrillation; bruit disappeared 6 days after first treatment; B. M. R. normal 12/28/43; later had duodenal ulcer and back strain; 2/12/46 blood cholesterol 269 mg., serum iodine 4.9 micrograms
7. A. S.	28	♀	60 3x	+28	61	30 mc.	12/28/43	....	0.50	4 wks.	+5	65	1 x	B. M. R. —10 by 1/25/44; last seen 4/3/45
8. L. S.	42	♂	60 3x	+44	56	43 mc.	1/19/44	18%	0.71	3 mos.	+1 11/6/45	66	1 x	See details in case report and chart 2
9. L. Z.	36	♀	50 2½x	+27	48	37 mc.	2/11/44	26%	0.74	4 wks.	+28 10/9/45	47	1 x	Acute streptococcic tonsillitis 3 days after dose
10. L. J.	33	♀	40 2x	+22	44	23 mc.	3/11/44	81%	0.57	2 mos.	+6 1/29/46	45	1½ x left lobe	Subtotal thyroidectomy 1939; recurrence 1943; thyroid mass larger after dose; B. M. R. —3 May 1944
11. J. B. I.	50	♂	60 3x 40 2x	+63	60	38 mc. 25 mc. 48 mc.	5/23/44 7/ 8/44 5/ 3/45	22% 38% 74%	0.63 1.20	3 mos.	+11 1/15/46	69	1 x	Biopsy of thyroid while toxic, 5/20/44: biopsy of thyroid before third dose showed fibrosis but no sign of cancer
12. H. R.	37	♀	40 2x	+40	49	27 mc.	8/ 4/44	....	0.54	1 mo.	—18 11/6/45	56	1 x	Allergic person; well in 4 weeks and in myxedema 3 months after dose; see details in case report and chart 3
13. A. J.	35	♀	60 3x	+50	57	24 mc. 29 mc. 54 mc.	8/26/44 8/28/44 10/27/44	....	0.4 0.8	.....	+26 10/9/45	73	1 x	Observed one month on bed rest without treatment; improved by November 1944; thyroid normal through 1945
14. H. D.	33	♀	30 2x	+28	69	36 mc.	11/ 3/44	17%	1.20	2 mos.	0 1/29/46	72	1 x	Subtotal thyroidectomy 1933; nausea, vomiting and swollen thyroid after dose
15. J. S.	40	♀	40 2x	+26	56	45 mc.	12/ 5/44	86%*	1.12	3 wks.	—23 12/18/45	67	1½ x	Subtotal thyroidectomy in 1941; recurrence in 1944; rapid response after dose; well through 1945
16. M. R.	37	♀	60 3x	+36	60	52 mc.	12/ 8/44	34%*	1.00	2 wks.	— 8 4/16/46	70	1 x	See details in case report and chart 4
17. K. W.	63	♀	40 2x	+25	..	40 mc.	12/13/44	61%*	1.00	2 mos.	—1 7/10/45	..	1 x	Subtotal thyroidectomy 1937; x-ray treatment 1943 while on iodine; gradual response
18. J. P. M.	43	♀	45 2½x	+40	72	36 mc.	12/28/44	Acute pyelitis	0.80	6 wks.	—13 2/5/46	90	1 x	No response to thiouracil and other treatments; severe ophthalmopathy lessened gradually
19. M. W.	51	♂	60 3x	+30	56	43 mc.	1/10/45	23%*	0.71	2 mos.	—7 1/22/46	64	1 x	Obvious response in 10 days; gained 9.7 Kg. in 3 months after dose; radiation sickness
20. H. O.	49	♂	60 3x	+52	72	45 mc. 40 mc.	2/15/45 4/11/45	9% 100%	0.75	4 mos.	+1 12/17/45	78	1 x	Member of goitrous family; sensitive to iodine; severe radiation sickness; effect probably from first dose only
21. M. B. L.	34	♀	60 3x	+32	61	49 mc.	3/ 2/45	41%	0.70	5 mos.	—13 1/22/46	63	1 x	Long course of medical treatment; moderate exophthalmos; gradual response in 5 months
22. J. J. B.	39	♂	60 3x	+54	61	44 mc.	3/ 9/45	21%	0.75	6 wks.	—15 2/5/46	72	2½ x	House staff views with skepticism; dramatic response in 4 to 6 weeks

* Percentage in two days.
† Dr. Wendell C. Peacock made these determinations.

discover the amount needed to produce total thyroid inactivity (myxedema). With this in mind the first doses were usually less than 0.5 mc. per estimated gram of thyroid tissue. Later these were increased to between 0.5 and 1.0 mc. of 12-hour iodine per estimated gram of thyroid tissue. The average total dose per patient became 40 to 50 mc. and the largest single dose given has been 79 mc., which was about 0.8 mc. per estimated gram of thyroid tissue.

REPORT OF CASES [14]

CASE 1.—E. W., a man aged 49, a railroad agent who had been thyrotoxic since 1928, had 120 Gm. of thyroid removed in the Massachusetts General Hospital in 1930 after an iodine preparation; the postoperative course was stormy because of pulmonary collapse and edema. Through 1931, 1932 and 1933 he was moderately toxic despite taking iodine, as Lugol's solution, at least 10 drops daily. In June and August 1933 he was given roentgen therapy with a daily dose of 200 roentgens measured in air over a 10 cm. square field to alternating sides of the neck. A total of 800 roentgens was given to each side of the neck in eleven days. The voltage used was 200 kilovolts and the filter used was 0.5 mm. of copper and 4.0 mm. of aluminum. On three subsequent days he received another 800 roentgens to the posterior part of the neck. The target skin distance was 50 cm. Although the mass of tissue decreased in size, there was little decrease in his hyperthyroidism. He was not seen again in our clinic for ten years, and then in the spring of 1943 he returned, obviously toxic. He said that in 1941 he had been in a veterans' hospital but refused operation. On May 11, 1943 the basal metabolic rate was plus 36 and it was estimated that he had 40 Gm. of recurrent thyroid tissue. The eye signs were moderate. On May 18 he took 14 mc. of radioactive iodine and excreted in successive twenty-four hour intervals 14, 8, 2 and 1 per cent for a total of 25 per cent in four days. After an initial rise to plus 50 on June 1, the basal metabolic rate declined steadily to minus 12 by July 17. On August 21 the basal metabolic rate was plus 7 and the patient was delighted with the results of treatment. He had gained weight, the pulse was slower, the diarrhea had stopped, the eyes were almost normal in appearance and the thyroid was definitely smaller; in fact, it was difficult to feel any tissue. On September 24 a second dose of 20 mc. was given. This time at least 95 per cent of the dose was excreted in the urine in the three day period, suggesting that his thyroid handled iodine like a normal gland.[5] Owing to the small retention of radioactive iodine by the gland, this second radiation dose was unimportant. Throughout the remainder of 1943 he considered himself well and had normal basal metabolic rates. In 1944 he was so well that he came to the clinic only twice for tests. On Feb. 5, 1946 he was working regularly as a freight agent and had a basal metabolic rate of plus 8 after driving in 18 miles for the test. There were no signs of toxicity, and no thyroid tissue was felt.

CASE 2.—M. M., a Negro woman aged 38, had a huge symmetrical goiter with a bruit, definite exophthalmos and other signs of severe toxicity. In 1934 she had been operated on at the Peter Bent Brigham Hospital for multiple nontoxic adenomas of the thyroid. Thereafter she was well until 1939. From then through 1942 the signs of toxicity gradually developed, but no goiter was noticed by her. By February 1943 eye signs were first noted by the patient and her doctor. In March she was given six diathermy treatments to her neck, and immediately after this her neck swelled until a large goiter could be recognized at a distance. When first seen by us it was estimated to weigh 120 Gm. She had a basal metabolic level of plus 50 and on June 2, 1943 she received the first dose of 15 mc. After an increase in the basal metabolic rate to plus 65 the rate fell to plus 20 by June 28. By August 15 the metabolic rate was still elevated and she had shown little response, so she was given a second dose of 53 mc. on August 17. Thereafter she was nauseated for twenty-four hours. She excreted in successive twenty-four hour intervals 13, 14 and 8 per cent, or a total of 35 per cent. The basal metabolic rate dropped to minus 14 by August 31. She seemed better, and the gland decreased in size. However, in the month of September the metabolic rate went up and she was obviously toxic. A third dose of 79 mc. was given on September 29. Nausea and also fever upset the patient, but she recovered in three days and began to improve. In successive twenty-four hour intervals she excreted 27, 18 and 4 per cent for a total of 49 per cent in three days. By November the basal metabolic rate had dropped to minus 13 and she showed clinical evidence of the improvement by a gain in strength and weight and a decrease in the size of the goiter, which had become much firmer—almost hard—and estimated to weigh 45 Gm.

Throughout 1944 (chart 1) the patient continued to have normal or low metabolic rates, but the goiter persisted as a hard mass two to three times normal size and definite eye signs persisted. Despite the low basal metabolic rates she was judged to be in active disease. She was alternating at a job with her goiterous sister when seen on Jan. 9, 1945. The goiter was just visible, and a 2 cm. nodule had developed in the upper right lobe. She was then judged to be nontoxic,

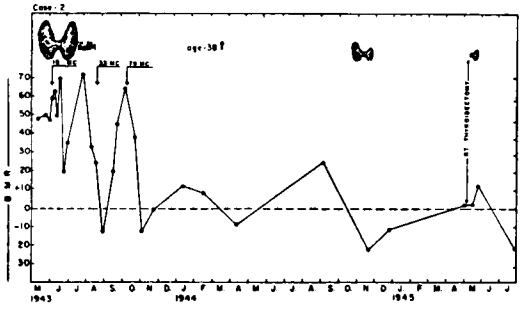

Chart 1.—Course of patient 2, who received three doses of radioactive iodine.

with pulse rate 60 and weight 53.9 Kg., a total gain of 6.9 Kg. Removal of the right lobe with the nodule was advised and on May 17 she entered the metabolic study wards and first had a tracer dose of 8-day (I^{131}) iodine and excreted 37 per cent and 4 per cent in two successive twenty-four hour intervals.

On May 19, without specific antithyroid medication, Dr. Robert Linton removed the right lobe. The operation was difficult because of fibrous adhesions and scar tissue. Histologic section of this tissue showed a background of dense fibrosis with islands of small follicles lined with cells of increased height and containing little colloid. Giant nuclei were present. The patient made a rapid recovery and left the hospital on the fifth day after operation. On subsequent visits to the clinic she has considered herself well. The basal metabolic rate on Feb. 21, 1946 was plus 12, and she seemed normal.

CASE 8.—L. S., a man aged 42, a taxi driver, entered the hospital Jan. 5, 1944 with classic symptoms and signs of moderately severe hyperthyroidism of six months duration. The thyroid was symmetrically enlarged to three times normal, and there was a large bruit. The eye signs were minimal. The basal metabolic rates were plus 44 to 52. On January 19 he drank 48 cc. of a solution containing 43 mc. and that evening experienced nausea and the following day fever to 102 F. (oral). With this upset he said that the thyroid increased in size. By January 21 he was much better and the temperature returned to normal. Excretion of radioactivity in the first day was 6 per cent, second day 7 per cent, third day 3 per cent and fourth day 2 per cent, a total of 18 per cent.

14. A summary of the 22 cases is given in table 2. Space does not permit the inclusion of histories of all 22 cases in THE JOURNAL. Histories of all cases, however, will appear in the reprints. The following 5 cases have been selected as illustrating significant points in the treatment of hyperthyroidism with high dosage of radioactive iodine: Case 1. The first case treated in this series. Case 2. A huge goiter that required three doses of radioactive iodine. A hard nodule developed that was removed and proved to show fibrosis. Case 8. Response to a single dose of radioactive iodine, followed by a return to a euthyoid state. Case 12, in which clinical myxedema developed and persisted for over a year. Case 16, in which sensitiveness to both thiouracil and iodine was shown, with good response later to radioactive iodine.

The response of this patient (chart 2) has been very good and at the visit on Nov. 11, 1945 his basal metabolic rate was plus 1.

CASE 12.—H. R., a woman aged 37, a housewife, was admitted to the wards on July 21, 1944 with moderate hyperthyroidism, moderate eye signs and a thyroid that was symmetrically enlarged to two and one-half times normal. A bruit was present. The basal metabolic rate ranged from plus 30 to 40. Fortu-

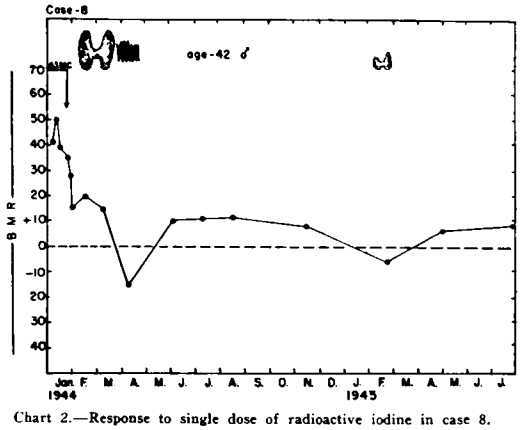

Chart 2.—Response to single dose of radioactive iodine in case 8.

nately only one dose of 5 drops of saturated solution of potassium iodide was given on July 28, so on the 4th of August 27 mc. of radioactive iodine was given by mouth. The patient improved rapidly and by September 5 the thyroid seemed normal, the eyes were normal and the metabolic rates were normal. Through the autumn she gradually felt cold and sluggish, and by November 28 the basal metabolic rate was minus 20 and she was in a state of moderate myxedema. No treatment for this was given, but continued observations confirmed this opinion. By Feb. 6, 1945 she had gained 8.6 Kg. and suffered from the cold. Through 1945 she continued to feel sluggish and tired easily, and the basal metabolic rate continued low and the thyroid was not palpable. Chart 3 depicts her course. She has not taken thyroid.

CASE 16.—M. R., a woman aged 37, a housewife, was referred to us by Dr. R. H. Williams of the Boston City Hospital. Her favorable response to thiouracil had previously been reported (Williams and Bissell,[15] case 5) but in July and again in November 1944 she developed acute febrile, toxic reactions to thiouracil and thiourea, so another form of treatment became necessary. Five drops of saturated solution of potassium iodide twice daily was tried, but this caused an extensive dermatitis with fever, a reaction that lasted about a week.

When first seen by us on Dec. 5, 1944 she was in active thyrotoxicosis with the basal metabolic rate plus 36 and a diffusely enlarged thyroid without a bruit. The eyes showed lid edema, slight exophthalmos and lid lag. The gland was estimated to be three times normal size (45-60 Gm.). December 8 she swallowed 52 mc. of radioactive iodine. That night she vomited and noted pressure in the neck. Excretion for zero to twenty-four hours was 28 per cent and from twenty-four to forty-eight hours 6 per cent, totaling 34 per cent. On December 19 the basal metabolic rate was minus 2 and she felt much better. Subsequently she showed a weight gain and a decline into a myxedematous state, but without medication she returned to low normal basal metabolic rates. The thyroid was not palpable. Chart 4 best depicts her course.

COMMENT

These 22 cases represent our three years' experience in treating hyperthyroidism only with large doses of radioactive iodine. If we try to summarize the results we can say that, as with other methods of treatment, there are good results, surprising effects and some poor results and disappointments. Obviously such a small group does not lend itself to statistical analysis. Of the 22 patients who originally had goiters at least two to three times the size of a normal thyroid, 21 (all except patient 2) now have no goiter, or a thyroid that is just palpable. We can point out that, of 12 patients treated before Aug. 15, 1944, 11 are well and show no signs of toxic goiter; the 12th, patient 9, continues mildly thyrotoxic. Patient 2 originally had a huge goiter and developed a hard, nodular right lobe that was removed by hemithyroidectomy. The histologic appearance of this gland was of fibrosis engulfing scattered acini with high columnar cells. No evidence of malignant disease was seen. The reduction in the amount of hyperplastic tissue seems to explain the response to treatment. However, the remaining thyroid follicles appear to be hyperplastic, so that it seems reasonable to conclude that radioactive iodine does not affect the original stimulus causing hyperthyroidism but acts only to destroy the overfunctioning parenchyma.

The basal metabolic curves of 14 patients who received a single dose of radioactive iodine are recorded graphically in chart 5. The rate of response is in reasonable relation to the probable loss of previously formed thyroxin. Our composite curves may be compared to the iodine-response curve [16] and the thiouracil-response curve,[17] both of which have been interpreted as thyroxin-decay curves. The average length of time for the complete response to the radioactive iodine treatment was about seven to eight weeks, which is longer than the time required for the response to iodine or thiouracil.

Of the 10 patients treated since Aug. 15, 1944,[18] all have made a good response to treatment, although the basal metabolic rate of patient 13 has continued above normal, but the patient has no goiter and insists that she is well. By a response to treatment we mean that the patients have felt better, gained weight and had an

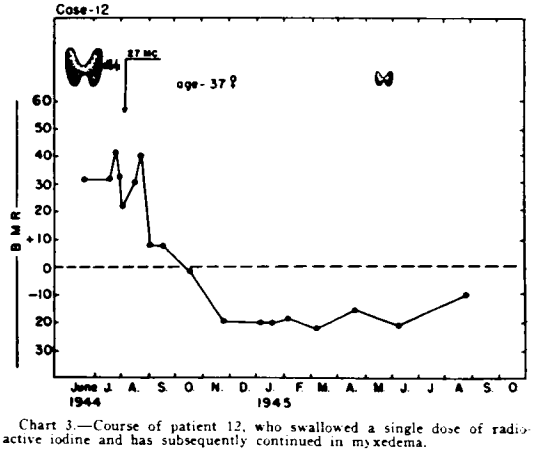

Chart 3.—Course of patient 12, who swallowed a single dose of radioactive iodine and has subsequently continued in myxedema.

appreciable decrease in the size of the goiter, a persistent fall in their basal metabolic rate and a diminution in their eye signs. Improvement of the eyes has been

15. Williams, R. H., and Bissell, G. W.: Thiouracil in the Treatment of Thyrotoxicosis, New England J. Med. **228**: 97 (July 15) 1943.

16. Means, J. H., and Lerman, J.: The Curves of Thyroxine Decay in Myxedema and of Iodine Response in Thyrotoxicosis: Their Similarity and Its Possible Significance, Ann. Int. Med. **12**: 811 (Dec.) 1938.

17. Rawson, R. W.; Evans, R. D.; Means, J. H.; Peacock, W. C.; Lerman, J., and Cortell, R. E.: The Action of Thiouracil on the Thyroid Gland in Graves' Disease, J. Clin. Endocrinol. **4**: 1 (Jan.) 1944.

18. Twenty-five additional cases in which there has been response to treatment since March 1945 are not included in this report as the follow-up period has been too short.

least of all these responses. Of the 22 patients treated there was only 1 who had severe ophthalmopathy, and we believe that this decreased after the treatment with radioactive iodine. Another index of a favorable response has been the observations on the blood lipid fractions before and after treatment. Dr. F. F. Foldes [19] made these determinations in 3 cases, in all of which the plasma lipid values increased after treatment, parallel with the clinical improvement.

It is of note that 7 of our 22 patients (1, 2, 5, 10, 14, 15 and 17) had been previously operated on for

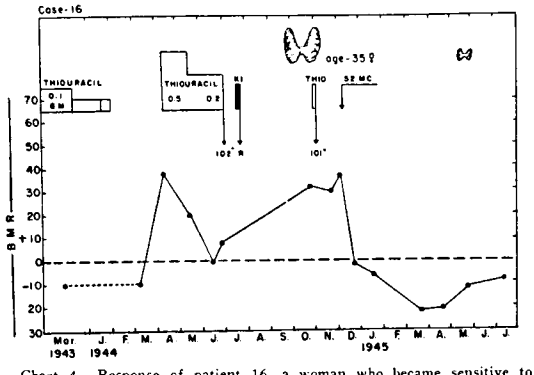

Chart 4.—Response of patient 16, a woman who became sensitive to thiouracil and iodine and has responded to a single dose of radioactive iodine.

hyperthyroidism and these 7 have responded very well to radioactive iodine treatment. Three (1, 3 and 17) of the 22 had received previous roentgen treatment by the usual external application without halting the disorder and yet in each a good result has been obtained with radioactive iodine. One patient, sensitive to both thiouracil and iodine, has had a good response and developed mild myxedema. Eight (2, 4, 5, 6, 7, 9, 11 and 13) of the 22 patients had not previously taken iodine; of these 8 patients 3 (2, 11 and 13) had the largest goiters in the entire group and required three doses at intervals of several months to control their thyrotoxicosis. The response to this form of radiation seems roughly in inverse proportion to the amount of tissue causing thyrotoxicosis. The larger goiters did not respond as quickly as the smaller.

The absence of ordinary iodine and yet the adequate response to radioactive iodine support our belief that ordinary iodine by mouth is not needed in conjunction with radioactive iodine therapy. However, it seems advisable to withhold ordinary iodine for several weeks before administering radioactive iodine in order to assure maximum uptake by the thyroid of the radioactive iodine. The lack of iodine in the gland may be a condition that favors a better response to radiation; possibly this links with the good effects seen from external roentgen treatment in the period before 1924, when iodine treatment became popular. We have as yet no comparative experiments demonstrating whether or not ordinary iodine started a few days after the radioactive iodine will hasten the response. Such a series is now under observation.

In 4 instances (cases 3, 12, 15 and 16) hypothyroidism, or evident myxedema, was produced. Although none of these 4 were treated with thyroid, 2 gradually returned to low normal basal metabolic rates. The approximate dosage of 1 millicurie per estimated gram of tissue in these 4 cases seems to be high, and yet we have tried this dosage in others without producing myxedema. The individual variation in absorption and excretion makes the matter of dosage selection uncertain.

Toxic reactions to large doses of radioactive iodine are very much like acute roentgen ray sickness. Nausea, vomiting, malaise and even slight increase in gland size and fever occurred and lasted two days at the most; the doses were 48 mc. or more in 4 of the 6 patients having radiation sickness. No subsequent ill effects or leukopenia have been observed. Malignant changes were not observed in the tissue removed in 2 cases, 1 as long as two years after this form of radiation.

SUMMARY AND CONCLUSION

1. In hyperthyroidism orally administered doses of radioactive iodine, carried in about 1 mg. or less of ordinary iodine, are concentrated largely in the thyroid gland. The beta rays from the radioactive iodine deliver within the thyroid an internal radiation which is physically similar to roentgen radiation. The radiation dose in a patient who swallowed 14 millicuries has been calculated as equivalent to approximately 3,490 roentgens, due to the 12-hour isotope.

2. Between May 1943 and March 1945, 22 patients having hyperthyroidism were treated with large doses of radioactive iodine. No other form of therapy was given.

3. Fourteen patients responded well to a single dose of radioactive iodine; 3 were given two doses and 5 were given three doses. Myxedema has followed this treatment in 4 patients. Two patients after treatment with this agent, though improved, still have mild hyperthyroidism.

4. Reactions which resembled roentgen ray sickness were observed in 6 patients following large doses of radioactive iodine. Fibrosis of the thyroid has been observed in biopsy of 2 patients after treatment.

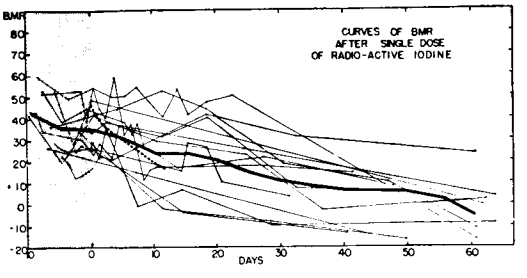

Chart 5.—Curves of basal metabolic rate after a single dose of radioactive iodine. The shaded area is before the treatment. The heavy black line is the average of fourteen curves. The dotted line is the ordinary iodine response curve of Means.

5. Patients who have not responded to other forms of treatment or have been sensitive to iodine or thiouracil have responded well to radioactive iodine. Ordinary iodine is not necessary with radioactive iodine treatment.

6. We believe that therapy with radioactive iodine can be added to the growing list of medical methods for the control of thyrotoxicosis.

266 Beacon Street, Boston 16.

19. Foldes, F. F., and Murphy, A. J.: The Distribution of Cholesterol, Cholesterol Ester and Phospholipid P. in Red Cells and Plasma of (1) Normal Subjects and (2) in Diseases of the Thyroid, to be published; Methods: Bloor, W. R.: J. Biol. Chem. **24**: 227, 1916; **24**: 447, 1916; **36**: 33, 1918. Fiske, C. H., and Subbarow, Yellapragada, ibid. **66**:375, 1925.